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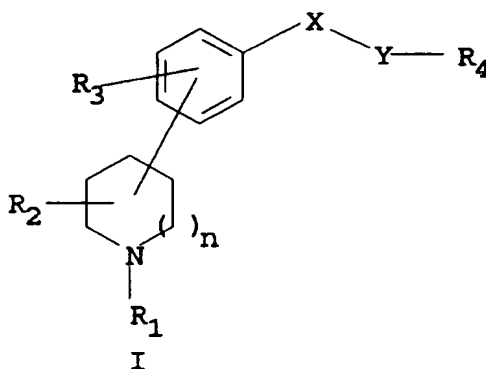
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**NL PT SE**(72) Inventor: **The designation of the inventor has**  
**not yet been filed**(54) **Piperidine derivatives as inhibitors of platelet aggregation and their preparation.**(57) **Compounds of formula I**

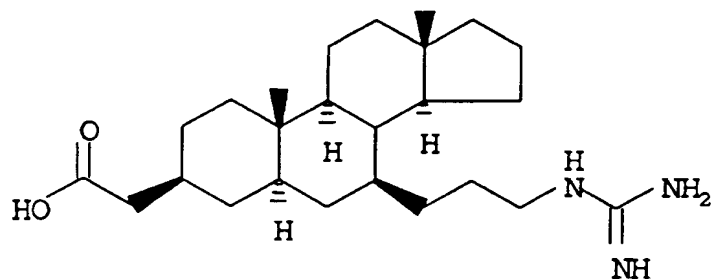
in which the substituents  $R_1$ - $R_4$ , X,Y and n have the given meaning, show an activity as inhibitors of platelet aggregation.

**EP 0 659 743 A1**

The instant invention is directed to heterocyclic compounds, their preparation and their use, in particular their use as inhibitors of platelet aggregation.

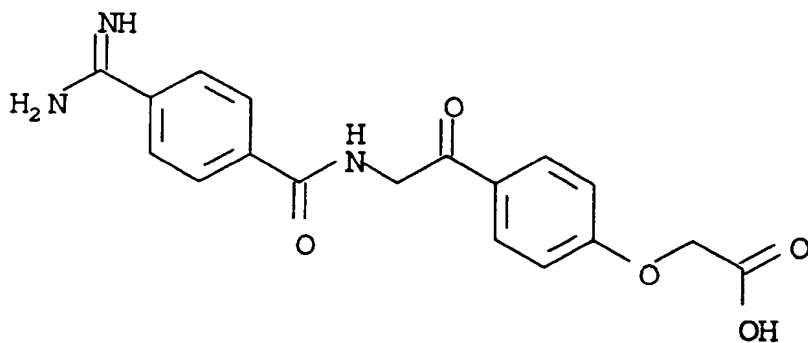
Known inhibitors of platelet aggregation have, for example, the following formulas:

1.



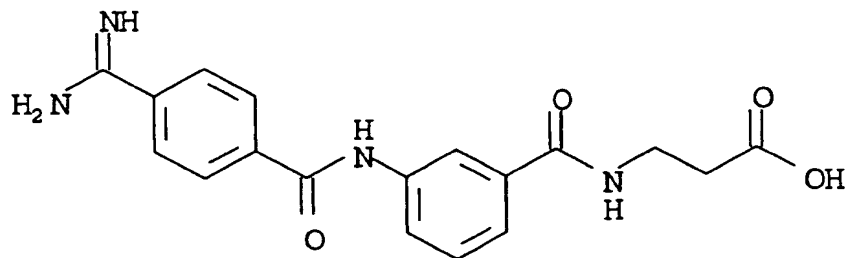
J. Amer. Chem. Soc., 1992, 114, 9699-9701.

2.



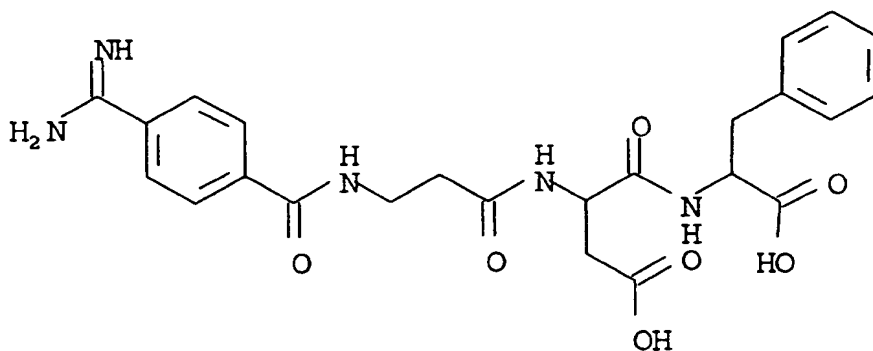
US Patent 5,039,805, 1991.

3.



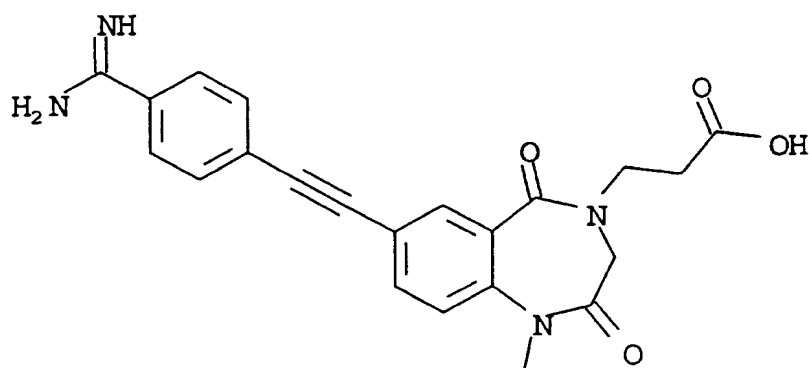
EP 0 483 667

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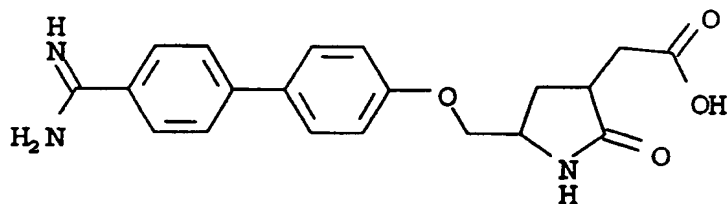
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J. Med. Chem., 36 (21), 3039-3049, 1993.

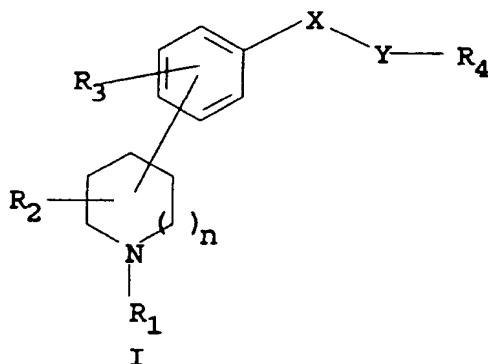
6.



EP 0 483 667

Surprisingly, it has now been found, that the heterocyclic compounds according to the instant invention have an activity as inhibitors of platelet aggregation.

Accordingly, the subject of the instant invention are compounds of formula I



wherein,

$R_1$  = H,  $C_1$ - $C_{10}$ -alkyl,  $C(=NH)-NH_2$ ,  $C(=NH)-NHR_5$  wherein  $R_5$  is  $C_1$ - $C_4$ -alkyl,  $C(=O)-C_1$ - $C_4$ -alkyl,  $C(=O)-C_1$ - $C_4$ -alkyl-aryl,  $C(=O)$ -aryl,  $C(=O)$ -substituted aryl,  $S(=O)_2$ - $C_1$ - $C_4$ -alkyl,  $S(=O)$ -aryl,  $S(=O)_2$ -aryl,  $S(=O)_2$ -substituted aryl;

$C(=O)-C_1$ - $C_{10}$ -alkyl- $NH_2$ ,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $NH-C_1$ - $C_4$ -alkyl,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $N(C_1$ - $C_4$ -alkyl) $_2$ ,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $NH-C(=O)-NH_2$ ,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $NH-C(=O)-NH-C_1$ - $C_4$ -alkyl,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $NH-(=NH)-NH_2$ ,  $C_1$ - $C_4$ -alkyl- $C(=NH)-NH_2$ ,  $C(=O)-C_1$ - $C_4$ -alkyl- $C(=NH)-NH_2$ ,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $NH-C(=NH)-NH-R_5$ , wherein  $R_5$  is as defined above;

$R_2$  = H, one, two or three substituents, which are the same of different, selected from the group consisting of  $C_1$ - $C_4$ -alkyl, OH,  $O-C_1$ - $C_4$ -alkyl,  $O-C(=O)-C_1$ - $C_4$ -alkyl,  $O-C(=O)-C_1$ - $C_4$ -alkyl-aryl,  $O-C(=O)-NH_2$ ,  $O-C(=O)-NH-C_1$ - $C_4$ -alkyl,  $O-C(=O)-NH$ -aryl,  $O-C(=O)-N(C_1$ - $C_4$ -alkyl) $_2$ ;

$R_3$  = H, one, two or three substituents, which are the same of different, selected from the group consisting of  $C_1$ - $C_4$ -alkyl,  $O-C_1$ - $C_4$ -alkyl, F, Cl, Br, OH,  $O-C(=O)-C_1$ - $C_4$ -alkyl,  $NH_2NH-C_1$ - $C_4$ -alkyl,  $N(C_1$ - $C_4$ -alkyl) $_2$ ,  $NH-C(=O)-C_1$ - $C_4$ -alkyl,  $NH-C(=O)$ -aryl,  $NH-C(=O)-NH_2$ , COOH,  $C(=O)-O-C_1$ - $C_4$ -alkyl,  $C(=O)-NH_2$ ,  $C(=O)-NH-C_1$ - $C_4$ -alkyl,  $C(=O)-N(C_1$ - $C_4$ -alkyl) $_2$ ,  $C_1$ - $C_4$ -COOH,  $C_1$ - $C_4$ -alkyl- $C(=O)-O-C_1$ - $C_4$ -alkyl;

X = O, S,  $C(=O)$ ,  $C(=S)$ ,  $CH-C_1$ - $C_4$ -alkyl,  $C(C_1$ - $C_4$ -alkyl) $_2$ , CHOH,  $((OH)-C_1$ - $C_4$ -alkyl);

Y =  $C_1$ - $C_{10}$ -alkyl,  $C_2$ - $C_{10}$ -alkenyl,  $C_2$ - $C_{10}$ -alkynyl,  $C_1$ - $C_4$ -alkyl-aryl,  $C_2$ - $C_6$ -alkenyl-aryl,  $C_2$ - $C_6$ -alkynyl-aryl,  $C_1$ - $C_4$ -alkyl-substituted aryl,  $C_1$ - $C_4$ -alkenyl-substituted-aryl,  $C_1$ - $C_4$ -alkyl-heteroaryl,  $C_1$ - $C_4$ -alkenyl-heteroaryl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

$R_4$  = H, one, two or three substituents, which are the same of different, selected from the group consisting of  $SO_3H$ ,  $C(=O)-R_6$ ,  $C_1$ - $C_{10}$ -alkyl- $C(=O)-R_6$ ,  $C_2$ - $C_{10}$ -alkenyl- $C(=O)-R_6$ ,  $C_2$ - $C_{10}$ -alkynyl- $C(=O)-R_6$ ,  $O-C_1$ - $C_{10}$ -alkyl- $C(=O)-R_6$ ,  $H-N-C(=O)-C_1$ - $C_{10}$ -alkyl- $C(=O)-R_6$ ,  $N(C_1$ - $C_4$ -alkyl)- $C(=O)-C_1$ - $C_{10}$ -alkyl- $C(=O)-R_6$ ,  $C(=O)-NH-C_1$ - $C_{10}$ -alkyl- $C(=O)-R_6$ ; wherein  $R_6$  is OH,  $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkyl-aryl, aryl, substituted aryl,  $NH_2$ ,  $NH-C_1$ - $C_4$ -alkyl,  $N(C_1$ - $C_4$ -alkyl) $_2$ ;

$n$  = 0, 1 or 2

as well as the physiologically tolerable addition salts thereof.

The above-mentioned term alkyl means radicals such as  $CH_3$ ,  $C_3H_7$ ,  $C_4H_9$  etc. which may also be branched e.g.  $(CH_3)_2CH$ .

The term alkenyl means an alkyl radical containing at least one double bond, e.g.  $-CH_2-CH=CH-CH_3$  etc.

The term alkynyl refers to an alkyl radical containing at least one triple bond such as  $-CH_2-C\equiv C-CH_3$ .

The term aryl refers to cyclic planar unsaturated radicals such as phenyl, naphthyl etc.

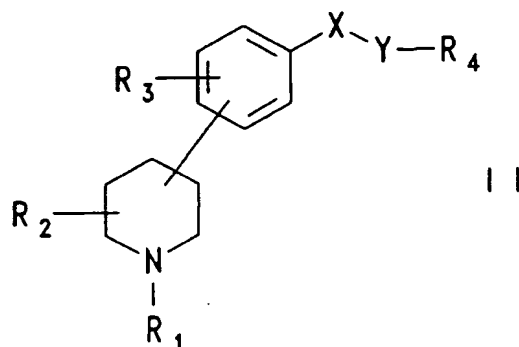
The term heteroaryl refers to cyclic, planar unsaturated radicals containing hetero atoms like N, S, O etc. Examples of hetero aryl residues are pyridyl, quinyl, thienyl etc.

The term substituted aryl means aryl radicals substituted by atoms or groups of atoms such as  $C_1$ - $C_4$ -alkyl, OH, COOH,  $C(=O)-O-C_1$ - $C_4$ -alkyl,  $NH_2$ ,  $O-C_1$ - $C_4$ -alkyl, Cl, Br, F.

The term substituted heteroaryl means heteroaryl radicals substituted by atoms or groups of atoms such as  $C_1$ - $C_4$ -alkyl, OH,  $O-C_1$ - $C_4$ -alkyl, COOH,  $C(=O)-O-C_1$ - $C_4$ -alkyl,  $NH_2$ , Cl, Br and F.

The physiologically tolerable addition salts of the compounds according to the instant invention are in particular salts with organic or inorganic acids, for example acetic acid, citric acid HCl or methylsulfonic acid.

Preferred are the compounds of the formula II



wherein,

$R_1$  = H, C<sub>1</sub>-C<sub>4</sub>-alkyl, C(=NH)-NH<sub>2</sub>, C(=NH)-NHR<sub>5</sub> wherein R<sub>5</sub> is as defined above, C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=NH)-NH<sub>2</sub>, C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=NH)-NH<sub>2</sub>;

$R_2$  = H, one or two substituents, which are the same or different, selected from the group consisting of C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C<sub>1</sub>-C<sub>4</sub>-alkyl, OH, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-aryl, O-C(=O)-NH-C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C(=O)-NH-aryl;

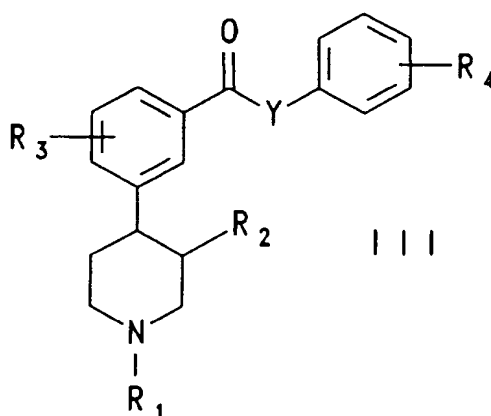
$R_3$  = H, one or two substituents, which are the same or different, selected from the group consisting of OH, O-C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl, F, Cl, Br, NH<sub>2</sub>, NH-C<sub>1</sub>-C<sub>4</sub>-alkyl, N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, NH-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl, NH-C(=O)-aryl, COOH, C(=O)-O-C<sub>1</sub>-C<sub>4</sub>-alkyl;

X = C=O, CHOH, C(OH)-C<sub>1</sub>-C<sub>4</sub>-alkyl, C(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, CH(C<sub>1</sub>-C<sub>4</sub>-alkyl);

Y = C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>2</sub>-C<sub>4</sub>-alkenyl, C<sub>2</sub>-C<sub>4</sub>-alkynyl, C<sub>1</sub>-C<sub>4</sub>-alkyl-aryl, C<sub>2</sub>-C<sub>4</sub>-alkenyl-aryl, C<sub>2</sub>-C<sub>4</sub>-alkynyl-aryl, C<sub>1</sub>-C<sub>4</sub>-alkyl-substituted aryl, C<sub>1</sub>-C<sub>4</sub>-alkenyl-substituted-aryl, C<sub>1</sub>-C<sub>4</sub>-alkyl-heteroaryl, C<sub>1</sub>-C<sub>4</sub>-alkenyl-heteroaryl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

$R_4$  = H, one or two substituents, which are the same or different, selected from the group consisting of SO<sub>3</sub>H and groups represented by C(=O)-R<sub>6</sub>, C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, C<sub>2</sub>-C<sub>4</sub>-alkenyl-C(=O)-R<sub>6</sub>, C<sub>2</sub>-C<sub>4</sub>-alkynyl-C(=O)-R<sub>6</sub>, O-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, NH-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, N-(C<sub>1</sub>-C<sub>4</sub>-alkyl)-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, C(=O)-NH-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, wherein, R<sub>6</sub> is as defined above.

Particularly preferred are the compounds of formula III



wherein,

$R_1$  = H, C<sub>1</sub>-C<sub>4</sub>-alkyl, C(=NH)-NH<sub>2</sub>, C(=NH)-NHR<sub>5</sub> wherein R<sub>5</sub> is as defined above, C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=NH)-NH<sub>2</sub>, C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=NH)-NH<sub>2</sub>;

$R_2$  = H, C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C<sub>1</sub>-C<sub>4</sub>-alkyl, OH, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-aryl, O-C(=O)-NH-C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C(=O)-NH-aryl;

$R_3$  = H, or a substituent selected from the group consisting of OH, O-C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-

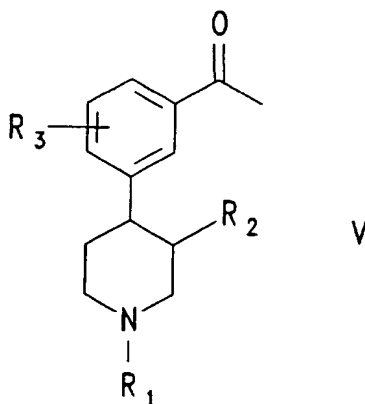
alkyl, F, Cl, Br, NH<sub>2</sub>, NH-C<sub>1</sub>-C<sub>4</sub>-alkyl, N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, NH-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl, NH-C(=O)-aryl, COOH, C(=O)-O-C<sub>1</sub>-C<sub>4</sub>-alkyl;

Y = C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>2</sub>-C<sub>4</sub>-alkenyl and C<sub>2</sub>-C<sub>4</sub>-alkynyl;

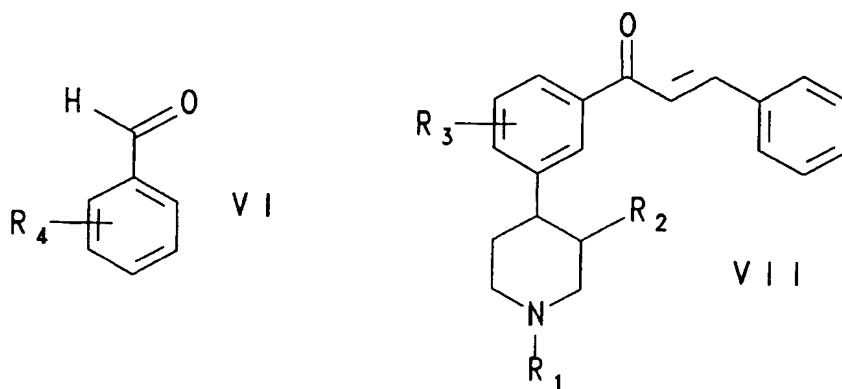
R<sub>4</sub> = H, or a substituent selected from the group consisting of SO<sub>3</sub>H, and groups represented by C(=O)-R<sub>6</sub>, C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, C<sub>2</sub>-C<sub>4</sub>-alkenyl-C(=O)-R<sub>6</sub>, C<sub>2</sub>-C<sub>4</sub>-alkynyl-C(=O)-R<sub>6</sub>, O-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, NH-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, N(C<sub>1</sub>-C<sub>4</sub>-alkyl)-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, C(=O)-NH-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, wherein, R<sub>6</sub> is OH, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyl-aryl, aryl, substituted aryl, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>4</sub>-alkyl), N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>.

The compounds of the present invention may contain asymmetric centers and therefore the invention encompasses all the stereoisomers in pure form or as mixtures.

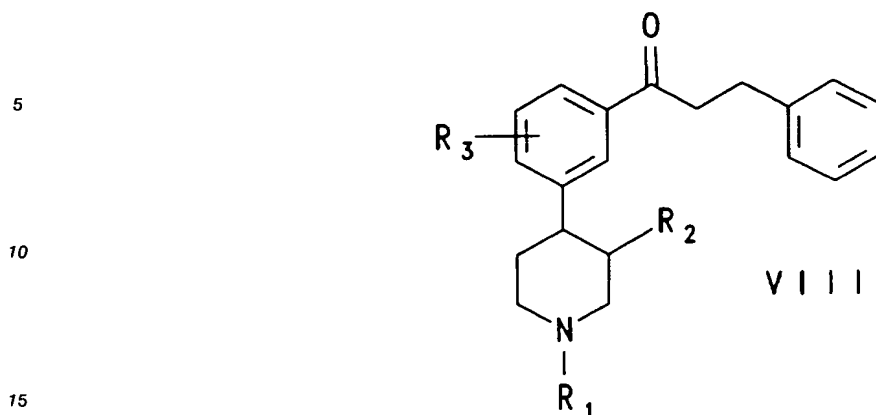
Another subject of the instant invention is a process for the production of a compound as claimed in one or more of claims 1-3, wherein a compound formula V



is reacted with a compound of formula VI to give a compound of formula VII



which in turn is optionally catalytically hydrogenated to a compound of formula VIII



wherein the substituents have the denotations as outlined above.

The preparation of compounds of formula V are known in the literature (R. G. Naik et al., Tetrahedron, 44, p 2081, 1988).

The compounds of the formula V when treated with the compounds of the formula VI preferably with bases such as sodium hydroxide 1-10 % in alcoholic solvents such as methyl alcohol give compounds of formula VII. Other bases such as sodium hydride in aprotic solvents such as dry N,N-dimethylformamide can also be used. The compounds of the formula VII can also be prepared by treating compounds of formula V with compounds of formula VI under acidic conditions such as mineral acids in alcoholic solvents or organic acids such as p-toluenesulfonic acids in non protic solvents such as benzene. The compounds of formula VIII are preferably prepared by catalytic hydrogenation of compounds of formula VII.

As already mentioned, the compounds according to the instant invention show an activity as inhibitors of platelet aggregation. Fibrinogen is a glycoprotein present as a normal component of blood plasma. It participates in platelet aggregation and fibrin formation in the blood clotting mechanism. When a blood vessel receives an injury the platelets binding to fibrinogen will initiate aggregation and form a thrombus. Interaction of fibrinogen with platelets occurs through a membrane glycoprotein complex gp. IIb/IIIa. Inhibitors of this interaction are useful in modulation of thrombus formation.

Another subject of the instant invention is the use of the compounds as described above as pharmaceuticals, as well as pharmaceuticals containing an amount of at least one of the compounds as described above, optionally together with physiologically tolerable carriers and/or excipients. The said pharmaceuticals are produced according to procedures known in the art.

Representative examples of preferred compounds of the present invention are given in Table 1 (refer to formula III, R<sub>1</sub> = Me, addition salts with HCl)

Table 1

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Compd. No.	R <sub>3</sub>	R <sub>4</sub>	R <sub>2</sub>	Y'	mp °C
1	2,4,6-(OMe) <sub>3</sub>	p-O-CH <sub>2</sub> -CO <sub>2</sub> Me	OH	CH = CH	145-146
2	2-OH, 4,6-(OMe) <sub>2</sub>	p-O-CH <sub>2</sub> -CO <sub>2</sub> Me	OH	CH = CH	213-214
3	3-OH, 4,6-(OMe) <sub>2</sub>	p-O-CH <sub>2</sub> CO <sub>2</sub> Me	OH	CH <sub>2</sub> CH <sub>2</sub>	203-205
4	2-OH, 4,6-(OMe) <sub>2</sub>	p-O-CH <sub>2</sub> CO <sub>2</sub> H	OH	CH = CH	233-234
5	2,4,6-(OMe) <sub>2</sub>	p-O-CH <sub>2</sub> -CO <sub>2</sub> H	OH	CH = CH	236-237
6	2-OH, 4,6-(OMe) <sub>2</sub>	p-O-CH <sub>2</sub> -CO <sub>2</sub> Me	H	CH = CH	217-218
7	2-OH, 4,6-(OMe) <sub>2</sub>	p-O-CH <sub>2</sub> -CO <sub>2</sub> Me	H	CH <sub>2</sub> CH <sub>2</sub>	194-195

Example: Preparation of compound 1 of table 1.

To a solution of the compound of formula V ( $R_1 = \text{Me}$ ,  $R_2 = \text{OH}$  and  $R_3 = 2\text{-OH}$ ,  $4,6\text{-(OMe)}_2$ ) (0.2 g) in 8 ml of 10 % NaOH solution in aqueous ethyl alcohol (1:1) is added a compound of formula VI ( $R_4 = \text{O-CH}_2\text{-COOH}$ ) (0.223 g, 2 equiv.) and the mixture is stirred for 1 h. To the reaction mixture is added another equivalent of the aldehyde and stirred for one more hour. The reaction mixture is cooled in an ice bath and neutralized by addition of acetic acid to a pH of 7 to 7.5. The product is filtered and washed with minimum quantity of water and dried, to give compound 4, yield, 0.2 g, mp  $233^\circ\text{-}234^\circ\text{C}$ . The compound 4 (0.5 g) is stirred in dry methyl alcohol with thionyl chloride (0.5 ml). After the addition is over the mixture is stirred at r.t. for one hour. The reaction mixture is worked up by pouring into water and basified by adding aqueous sodium carbonate and extracted with chloroform. The residue obtained after removal of chloroform is loaded on silica gel and eluted with 2 % MeOH in  $\text{CHCl}_3$  + 1 %  $\text{NH}_4\text{OH}$ . The product is converted into the hydrochloride salt by adding ethereal HCl, mp  $145\text{-}146^\circ\text{C}$ , yield, 0.3 g.

The compounds of the above invention are tested for platelet binding inhibitory activity in the following assays:

1. In-vitro Human Platelet Aggregation in PRP:

Blood is drawn from healthy human volunteers who had no medication for at least two weeks. 8.4 ml of venous blood are collected into 1.4 ml of ACD solution (citric acid 0.8 %, sodium citrate 2.2 %, hirudin 0.6 u/ml) and centrifuged for 10 min. at 120 g. The platelet rich plasma (PRP) is carefully removed and remaining blood is further centrifuged at 1200 g for 15 min. to separate platelet poor plasma (PPP).

For aggregation studies the aggregometer is adjusted by using PPP and PRP. ADP is then added to PRP which is kept at  $37^\circ\text{C}$  and stirred constantly at 1000 rpm. The aggregation of platelets causes an increase in transparency of PRP which is recorded.

2. Preparation of Gel Filtered Platelets (GFP):

Platelet rich plasma (PRP) is collected as mentioned in the above procedure. Its pH is adjusted to 6.5 with ACD solution and then centrifuged at 285 g for 20 min.. The resulting pellet is resuspended in Tyrode's buffer (NaCl, 7.01 g/l; KCl, 0.194 g/l;  $\text{NaHCO}_3$ , 1.01 g/l; Glucose, 1.09 g/l;  $\text{NaH}_2\text{PO}_4$ , 0.061 g/l; Hepes, 2.380 g/l; albumin, 3.5 g/l) and the platelet suspension is applied on to a  $^{\text{R}}$ Sepharose CL 20 column. Equilibrium and elution is done with Tyrode's buffer. Platelets are recovered in the void volume. Final platelet concentration is adjusted to  $4 \times 10^8$  platelets/ml.

For the aggregation studies, GFP in Tyrodes buffer is mixed with calcium chloride (final concentration  $0.5 \mu\text{M}$ ) and an agonist (ADP or Thrombin) with or without test compound (1 to  $300 \mu\text{M}$ ) and incubated at  $37^\circ\text{C}$  for 3 min.. After the addition of fibrinogen (final conc. 1 mg/ml) the aggregation is recorded.

Calculation of Results:

Aggregation maximum for PRP or GFP without any inhibitor is taken as 100 % aggregation and is compared with aggregation maximum of PRP or GFP incubated with the test compound.

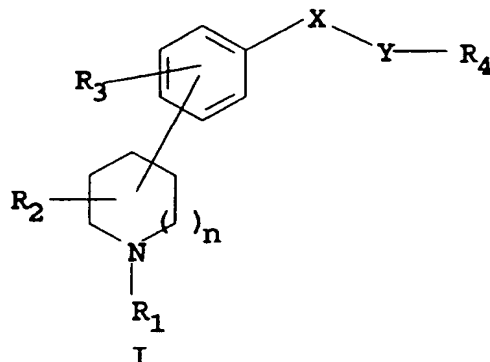
The results are summarized below:

Compound No. (see table 1)	$\text{IC}_{50}(\mu\text{M})$ Inhibitor of ADP induced Platelet aggregation
1	151.0 (PRP) 11.5 (GFP)
2	5.3 (PRP) 0.53 (GFP)
3	21.0 (PRP) 1.8 (GFP)
6	17.0 (PRP)
7	8.0 (PRP) 2.0 (GFP)



## Claims

## 1. Compounds of formula I



wherein,

$R_1 =$  H,  $C_1$ - $C_{10}$ -alkyl,  $C(=NH)-NH_2$ ,  $C(=NH)-NHR_5$  wherein  $R_5$  is  $C_1$ - $C_4$ -alkyl,  $C(=O)-C_1$ - $C_4$ -alkyl,  $C(=O)-C_1$ - $C_4$ -alkyl-aryl,  $C(=O)$ -aryl,  $C(=O)$ -substituted aryl,  $S(=O)_2$ - $C_1$ - $C_4$ -alkyl,  $S(=O)$ -aryl,  $S(=O)_2$ -aryl,  $S(=O)_2$ -substituted aryl;

$C(=O)-C_1$ - $C_{10}$ -alkyl- $NH_2$ ,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $NH-C_1$ - $C_4$ -alkyl,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $N(C_1-C_4-alkyl)_2$ ,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $NH-C(=O)-NH_2$ ,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $NH-C(=O)-NH-C_1-C_4$ -alkyl,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $NH-(=NH)-NH_2$ ,  $C_1$ - $C_4$ -alkyl- $C(=NH)-NH_2$ ,  $C(=O)-C_1$ - $C_4$ -alkyl- $C(=NH)-NH_2$ ,  $C(=O)-C_1$ - $C_{10}$ -alkyl- $NH-C(=NH)-NH-R_5$ , wherein  $R_5$  is as defined above;

$R_2 =$  H, one, two or three substituents, which are the same or different, selected from the group consisting of  $C_1$ - $C_4$ -alkyl, OH,  $O-C_1$ - $C_4$ -alkyl,  $O-C(=O)-C_1$ - $C_4$ -alkyl,  $O-C(=O)-C_1$ - $C_4$ -alkyl-aryl,  $O-C(=O)-NH_2$ ,  $O-C(=O)-NH-C_1$ - $C_4$ -alkyl,  $O-C(=O)-NH$ -aryl,  $O-C(=O)-N(C_1-C_4-alkyl)_2$ ;

$R_3 =$  H, one, two or three substituents, which are the same or different, selected from the group consisting of  $C_1$ - $C_4$ -alkyl,  $O-C_1$ - $C_4$ -alkyl, F, Cl, Br, OH,  $O-C(=O)-C_1$ - $C_4$ -alkyl,  $NH_2NH-C_1$ - $C_4$ -alkyl,  $NH-C(=O)-C_1$ - $C_4$ -alkyl,  $NH-C(=O)$ -aryl,  $N(C_1-C_4-alkyl)_2$ ,  $NH-C(=O)-NH_2$ ,  $COOH$ ,  $C(=O)-O-C_1$ - $C_4$ -alkyl,  $C(=O)-NH_2$ ,  $C(=O)-NH-C_1$ - $C_4$ -alkyl,  $C(=O)-N(C_1-C_4-alkyl)_2$ ,  $C_1$ - $C_4$ - $COOH$ ,  $C_1$ - $C_4$ -alkyl- $C(=O)-O-C_1$ - $C_4$ -alkyl;

$X =$  O, S,  $C(=O)$ ,  $C(=S)$ ,  $CH-C_1$ - $C_4$ -alkyl,  $C(C_1-C_4-alkyl)_2$ ,  $CHOH$ ,  $C(OH)-C_1$ - $C_4$ -alkyl;

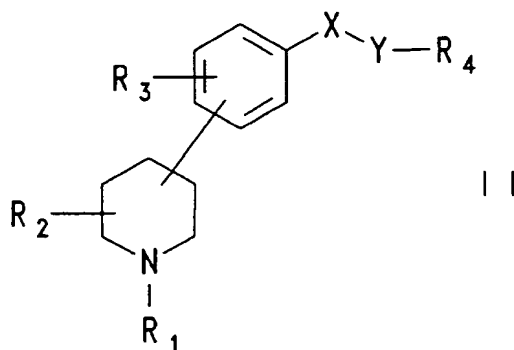
$Y =$   $C_1$ - $C_{10}$ -alkyl,  $C_2$ - $C_{10}$ -alkenyl,  $C_2$ - $C_{10}$ -alkynyl,  $C_1$ - $C_4$ -alkyl-aryl,  $C_2$ - $C_6$ -alkenyl-aryl,  $C_2$ - $C_6$ -alkynyl-aryl,  $C_1$ - $C_4$ -alkyl-substituted aryl,  $C_1$ - $C_4$ -alkenyl-substituted-aryl,  $C_1$ - $C_4$ -alkyl-heteroaryl,  $C_1$ - $C_4$ -alkenyl-heteroaryl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

$R_4 =$  H, one, two or three substituents, which are the same or different, selected from the group consisting of  $SO_3H$ ,  $C(=O)-R_6$ ,  $C_1$ - $C_{10}$ -alkyl- $C(=O)-R_6$ ,  $C_2$ - $C_{10}$ -alkenyl- $C(=O)-R_6$ ,  $C_2$ - $C_{10}$ -alkynyl- $C(=O)-R_6$ ,  $O-C_1$ - $C_{10}$ -alkyl- $C(=O)-R_6$ ,  $H-N-C(=O)-C_1$ - $C_{10}$ -alkyl- $C(=O)-R_6$ ,  $N(C_1-C_4-alkyl)-C(=O)-C_1$ - $C_{10}$ -alkyl- $C(=O)-R_6$ ,  $C(=O)-NH-C_1$ - $C_{10}$ -alkyl- $C(=O)-R_6$ ; wherein  $R_6$  is OH,  $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkyl-aryl, aryl, substituted aryl,  $NH_2$ ,  $NH-C_1$ - $C_4$ -alkyl,  $N(C_1-C_4-alkyl)_2$ ;

$n =$  0, 1 or 2,

as well as the physiologically tolerable addition salts thereof.

## 2. Compounds of formula II as claimed in claim 1,



wherein

$R_1 =$  H, C<sub>1</sub>-C<sub>4</sub>-alkyl, C(=NH)-NH<sub>2</sub>, C(=NH)-NHR<sub>5</sub> wherein R<sub>5</sub> is as defined in claim 1 C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=NH)-NH<sub>2</sub>, C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=NH)-NH<sub>2</sub>;

$R_2 =$  H, one or two substituents, which are the same or different, selected from the group consisting of C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C<sub>1</sub>-C<sub>4</sub>-alkyl, OH, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-aryl, O-C(=O)-NH-C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C(=O)-NH-aryl;

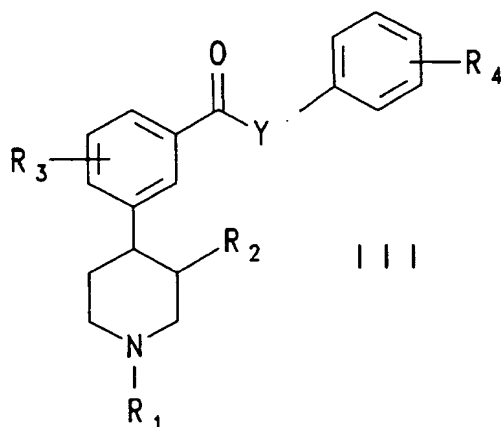
$R_3 =$  H, one or two substituents, which are the same or different, selected from the group consisting of OH, O-C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl, F, Cl, Br, NH<sub>2</sub>, NH-C<sub>1</sub>-C<sub>4</sub>-alkyl, N-(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, NH-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl, NH-C(=O)-aryl, COOH, C(=O)-O-C<sub>1</sub>-C<sub>4</sub>-alkyl;

$X =$  C = O, CHOH, C(OH)-C<sub>1</sub>-C<sub>4</sub>-alkyl, C(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, CH(C<sub>1</sub>-C<sub>4</sub>-alkyl);

$Y =$  C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>2</sub>-C<sub>4</sub>-alkenyl, C<sub>2</sub>-C<sub>4</sub>-alkynyl, C<sub>1</sub>-C<sub>4</sub>-alkyl-aryl, C<sub>2</sub>-C<sub>4</sub>-alkenyl-aryl, C<sub>2</sub>-C<sub>4</sub>-alkynyl-aryl, C<sub>1</sub>-C<sub>4</sub>-alkyl-substituted aryl, C<sub>1</sub>-C<sub>4</sub>-alkenyl-substituted-aryl, C<sub>1</sub>-C<sub>4</sub>-alkyl-heteroaryl, C<sub>1</sub>-C<sub>4</sub>-alkenyl-heteroaryl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

$R_4 =$  H, one or two substituents, which are the same or different, selected from the group consisting of SO<sub>3</sub>H and groups represented by C(=O)-R<sub>6</sub>, C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, C<sub>2</sub>-C<sub>4</sub>-alkenyl-C(=O)-R<sub>6</sub>, C<sub>2</sub>-C<sub>4</sub>-alkynyl-C(=O)-R<sub>6</sub>, O-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, NH-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, N(C<sub>1</sub>-C<sub>4</sub>-alkyl)-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, C(=O)-NH-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=O)-R<sub>6</sub>, wherein, R<sub>6</sub> is as defined in claim 1.

### 3. Compounds of formula III, as claimed in claims 1 or 2



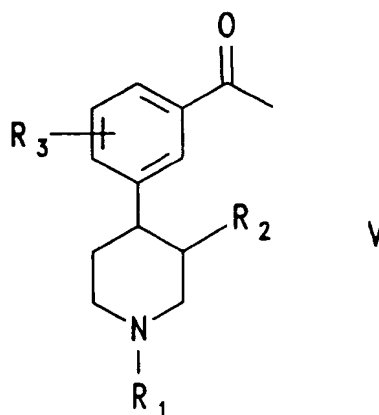
wherein,

$R_1 =$  H, C<sub>1</sub>-C<sub>4</sub>-alkyl, C(=NH)-NH<sub>2</sub>, C(=NH)-NHR<sub>5</sub> wherein R<sub>5</sub> is as defined in claim 1 C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=NH)-NH<sub>2</sub>, C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-C(=NH)-NH<sub>2</sub>.

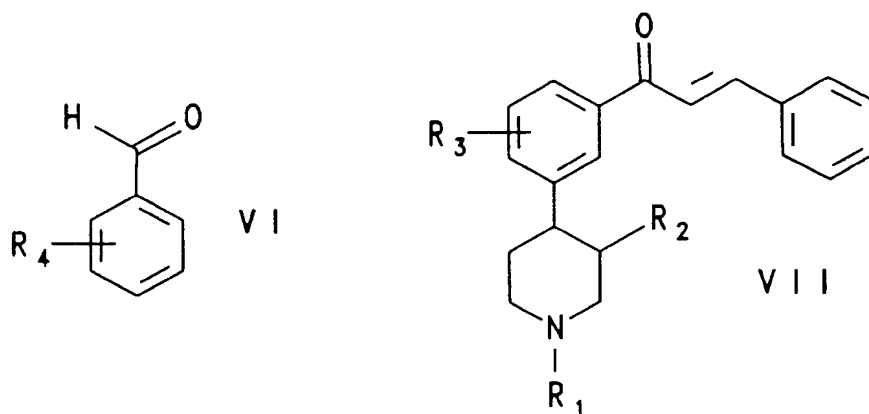
$R_2 =$  H, C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C<sub>1</sub>-C<sub>4</sub>-alkyl, OH, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl, O-C(=O)-C<sub>1</sub>-C<sub>4</sub>-alkyl-aryl, O-C-

- $(=O)-NH-C_1-C_4-alkyl$ ,  $O-C(=O)-NH-aryl$ ;  
 $R_3 =$  H, or a substituent selected from the group consisting of OH,  $O-C_1-C_4-alkyl$ ,  $O-C(=O)-C_1-C_4-alkyl$ , F, Cl, Br,  $NH_2$ ,  $NH-C_1-C_4-alkyl$ ,  $N(C_1-C_4-alkyl)_2$ ,  $NH-C(=O)-C_1-C_4-alkyl$ ,  $NH-C(=O)-aryl$ ,  $COOH$ ,  $C(=O)-O-C_1-C_4-alkyl$ ;  
 $Y =$   $C_1-C_4-alkyl$ ,  $C_2-C_4-alkenyl$  and  $C_2-C_4-alkynyl$ ;  
 $R_4 =$  H, or a substituent selected from the group consisting of  $SO_3H$ , and groups represented by  $C(=O)-R_6$ ,  $C_1-C_4-alkyl-C(=O)-R_6$ ,  $C_2-C_4-alkenyl-C(=O)-R_6$ ,  $C_2-C_4-alkynyl-C(=O)-R_6$ ,  $O-C_1-C_4-alkyl-C(=O)-R_6$ ,  $NH-C(=O)-C_1-C_4-alkyl-C(=O)-R_6$ ,  $N(C_1-C_4-alkyl)-C(=O)-C_1-C_4-alkyl-C(=O)-R_6$ ,  $C(=O)-NH-C_1-C_4-alkyl-C(=O)-R_6$ , wherein,  $R_6$  is OH,  $C_1-C_4-alkyl$ ,  $C_1-C_4-alkyl-aryl$ , aryl, substituted aryl,  $NH_2$ ,  $NH(C_1-C_4-alkyl)$ ,  $N(C_1-C_4-alkyl)_2$ .

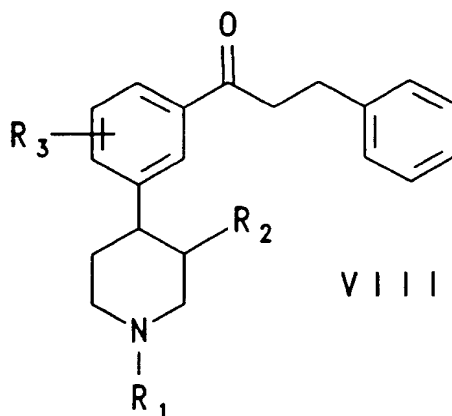
4. A process for the production of a compound as claimed in one or more of claims 1-3, wherein a compound formula V



is reacted with a compound of formula VI to give a compound of formula VII



which in turn is optionally catalytically hydrogenated to a compound of formula VIII



wherein the substituents  $R_1$  -  $R_4$  have the denotations.

5. The compounds as claimed in one or more of claims 1-3 as a pharmaceutical
6. The use of the compounds as claimed in one or more of claims 1-3 for the production of a pharmaceutical with an activity against platelet aggregation.
7. A pharmaceutical having an active amount of one or more compounds as claimed in one or more of claims 1-3 optionally together with physiologically tolerable carriers and/or excipients.
8. A process for the production of a pharmaceutical as claimed in claim 7, wherein at least one compound as claimed in claims 1-3 is brought, optionally together with physiologically tolerable carriers and/or excipients into a suitable form for administration.



European Patent  
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## EUROPEAN SEARCH REPORT

Application Number  
EP 93 12 0915

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,A	TETRAHEDRON vol. 44, no. 7 , 1988 , OXFORD pages 2081 - 2086 RAMACHANDRA G. NAIK E. A. *Page 2082 : formula 3* -----	1-3	C07D211/42 C07D211/30 A61K31/445
			TECHNICAL FIELDS SEARCHED (Int. Cl.6)
			C07D
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	3 May 1994	Luyten, H	
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons * : member of the same patent family, corresponding document			